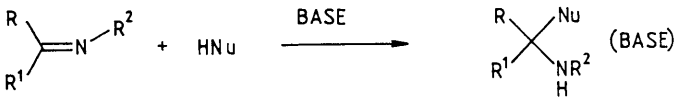
SUMMARY

Several theories of asymmetric autocatalysis have been developed in the last decades. The major goal of these studies was not to elucidate the exact mechanism of asymmetric autocatalysis but to survey various autocatalytic systems for their capacity to bifurcate into one predominate family of enantiomers. This would offer an explanation for the homochirality of amino acids and sugars now found in Nature. The existing models on asymmtric autocatalysis are reviewed in Chapter I and in the introduction of Chapter II. Experimental verification of these models is scarce although the models are abundant; only a few aspects of the models have an experimental basis and no reference is made to the actual structures of the various catalytic entities.

The aim of the present study is to obtain insight into the factors that influence asymmetric autocatalysis, and to verify these factors by experimental studies of asymmetric autocatalysis.

Asymmetric autocatalysis is defined as the process whereby a chiral chemical reaction product is the catalyst for its own formation from achiral reactants. The implications of this definition are treated in detail in Chapter II. A model based on a catalytic stereoselective synthesis using achiral reactants is used as a starting point. With this model we have shown that simple asymmetric autocatalysis cannot preserve the initial enantiomeric excess. Therefore we have pointed out and demonstrated the necessity for considering extra factors apart from autocatalysis and catalyst stereoselectivity in order to make autocatalysis truly asymmetric. These factors, crystallization and association, very common to organic reactions, are crucial for asymmetric autocatalysis.

Out of the large pool of potentially autocatalytic reactions we have restricted ourselves to base-catalyzed reactions. The base-catalyzed addition of nucleophiles to imines as shown in Scheme 1 is susceptible to autocatalysis.



Scheme 1: The addition of nucleophiles to imines.

An example of a reaction that fits in this scheme is the addition of naphthols to imines (Chapter III). The product of this addition reaction is an

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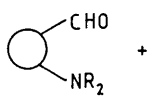

Scheme 2: The

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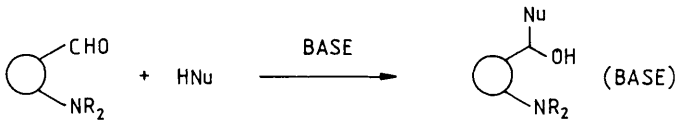
amine, which could be a more effective catalyst than the starting amine. Betti reported autocatalysis in the addition of β-naphthol to N-(benzylidene)aniline but we were unable to reproduce this result. A possible explanation for this contradiction could be traces of basic impurities in the starting materials used by Betti. In the case of N-(benzylidene)methylamines some autocatalysis was observed but the reaction was too slow to be useful for a study of asymmetric autocatalysis. Effective autocatalysis is blocked by the acidic naphthol group.

Another reaction that fits scheme 1 is the addition of hydrogen cyanide to imines (Chapter IV). The product of this reaction is optically active if quinine is used as a catalyst. This demonstrates that the reaction is catalyzed by quinine. However, the reaction can also be performed without added base. This could be the result of a fast autocatalytic reaction or a non-catalyzed reaction. Experiments with optically active product have shown the reaction to be autocatalytic but the induction was low. This is in agreement with the theoretical model we have presented in chapter II.

Other nucleophiles such as thiols, phosphonates, ketones or active methylene compounds were not suitable for the study of asymmetric autocatalysis. The products showed no autocatalytic activity or the reaction was hampered by side reactions (Chapter VI).

Another scheme which is prone to autocatalysis is the addition of nucleophiles to amino aldehydes (Scheme 2).



Scheme 2: The addition of nucleophiles to amino aldehydes.

In this scheme an amino aldehyde is converted into an amino alcohol. This is a potentially bifunctional catalyst which could serve as an efficient autocatalyst.

An example of a reaction that fits this scheme is the addition of phosphonates to amino aldehydes. Unfortunately no autocatalysis could be detected in the addition of 0,0-dimethylphosphonate to 2-pyridinecarboxaldehyde. The product is too weakly basic to catalyze its own formation. The addition of 0,0-dimethylphosphonates to amino aldehydes is intramolecularly catalyzed and this leaves no room for autocatalysis (Chapter VI).

The addition of diethylzinc to amino aldehydes could also fit in this scheme (Scheme 2). The addition of diethylzinc to aldehydes is catalyzed by amino zinc alkoxides. These zinc alkoxides are dimeric in solution and are responsible for the amplification of ee in the reaction. The addition of diethylzinc to pyridinecarboxaldehydes and amino aldehydes, however, did not yield optically active products. The corresponding amino zinc alkoxides are good catalysts for the addition of diethylzinc to benzaldehyde. We therefore proposed an alternative mechanism for the addition; intramolecular amino-catalyzed addition of diethylzinc to the aldehyde group. This renders the system unsuitable for the study of asymmetric autocatalysis.

Asymmetric autocatalysis is not an exotic theoretical model devoid of experimental verification. It is more likely that a large number of reactions show autocatalysis or some other influence by the product. Asymmetric autocatalysis requires extra factors, apart from autocatalysis and catalyststereoselectivity to proceed in a truly, asymmetric fashion. An experimental condition that favors asymmetric autocatalysis is the use of concentrated reaction media, which enhances the possibility of amplification of ee in the reaction. This excludes systems that require catalysis by base only. An area with prospects for asymmetric autocatalysis and open to further research is diastereoselective autocatalysis.

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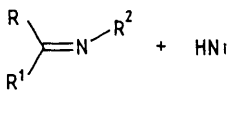

Schema 1: Algemeer
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Een reaktie